REMARKS

Status Summary

Claims 74-79, 81-87, and 89-96 are under examination. The remaining of claims 1-96 are withdrawn from consideration as being directed to non-elected inventions. The rejection of claims under 35 U.S.C. § 112, second paragraph is withdrawn based on previously submitted arguments and amendments. The rejection of claims under 35 U.S.C. § 112, first paragraph, as allegedly non-enabling for methods comprising administration of RITUXAN® is also withdrawn based on clarification of RITUXAN® as rituximab. Claims 81-82, 84, 86, and 90 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled based on a perceived non-availability and reproducibility of the rituximab antibody. Claims 74-79, 81-87, and 89-96 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Alas et al. (1998) *Blood* 92:601A in view of Levy et al. (1994) *J Clin Invest* 93:424-428 and U.S. Patent No. 6,183,744 to Goldenberg.

Reconsideration in view of the following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

Claims 81-82, 84, 86, and 90 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly being non-enabled based on a perceived non-availability and reproducibility of the rituximab antibody. In particular, the examiner contends that the transfectoma of American Type Culture Collection (ATCC) Deposit Number 69119 is not identifiable in the ATCC on-line catalog and that it is uncertain whether the rituximab sequence disclosed in U.S. Patent No. 5,736,137 is complete. Official action, page 3, item 7. This rejection is respectfully traversed.

Cells expressing the RITUXAN® (rituximab) antibody are publicly available as deposit number 69119 from the American Tissue Type Collection (ATCC). In support thereof, a receipt issued by the ATCC to confirm receipt of the deposit is submitted herewith.

In addition, the complete sequence of the rituximab antibody is disclosed in U.S. Patent No. 5,736,137. In particular, the examiner's attention is directed to Figures 3A-3F, wherein the tandem chimeric antibody expression vector further comprising murine light and heavy chain variable regions is disclosed, which sequence corresponds to anti-CD20 in TCAE 8 as deposited.

Based on the foregoing, this rejection of claims is believed to be rendered moot, and withdrawal of the rejection of claims 81-82, 84, 86, and 90 under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Notwithstanding the foregoing, the applicant recently contacted the ATCC by telephone. The applicant was advised that the ATCC would rectify the non-listing of Deposit Number 69119 in "a few weeks." Upon filing this response, the applicant will contact the examiner to discuss this issue.

Rejection of Claims Under 35 U.S.C. § 103(a)
Based on Alas in view of Levy and Goldenberg

Claims 74-79, 81-87, and 89-96 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Alas et al. (1998) *Blood* 92:601A in view of Levy et al. (1994) *J Clin Invest* 93:424-428 and U.S. Patent No. 6,183,744 to Goldenberg. The examiner continues to assert that "it would have been obvious to combine an anti-IL-10 antibody wherein removal of IL-10 results in abolishing the effects of bcl-2 by blocking cell death and adding C2B[8] to sensitize the 2F7 cells." Official action, pages 3-5, item 8. The examiner also dismisses previously submitted arguments to overcome the rejection as an improper attempt to argue the references individually where the rejection is based on a combination of the references. Official action, pages 3-5, item 8. This rejection is respectfully traversed based on the arguments set forth below.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicant responds that the examiner has not met this burden based on a failure to identify a specific suggestion or motivation to perform the claimed invention. Applicant further responds that the unexpected results of the present inventive method support the non-obviousness of the claimed combination therapy.

I. The Cited References Lack A Specific Suggestion Or Motivation To Perform The Claimed Combination

With regard to the first of the above-noted factors, suggestion or motivation to combine, such motivation may be found "where there is some teaching, suggestion, or motivation ... either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01 (citing *In re Kotzab*, 217 F.3d 1365, 1370 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)). Not only must such motivation be present, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added) (citing *In re Raynes,* 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The fact that the prior art teaches individual elements of the claimed invention that are generally known or within the capabilities of one with knowledge in the art is not, however, sufficient to establish a *prima facie* case of obviousness without any specific teaching or suggestion for making the combination. Accordingly, in a proper analysis of obviousness, the level of knowledge of one with ordinary skill in the art cannot be substituted for a clear suggestion to make a combination. *See A-Site Corp. v. VSI International Inc.,* 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Therefore, the examiner is required to show how and why the applicant would have been motivated to combine the references in the manner combined by the examiner.

Though the motivation to combine prior art does not have to be expressly stated in the references themselves, "the examiner must present a convincing line of reasoning" for a proper conclusion that an invention is obvious in view of prior art. *See In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). *See also, Ex parte Clapp,* 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985). When relying on a "scientific reasoning" rationale for combining references, the examiner must provide evidentiary support for the existence and meaning of that scientific theory. *See, In re Grose,* 592 F.2d 1161, 201 USPQ 57 (CCPA 1979).

Initially, with regard to the examiner's contention that the applicant has improperly argued the references individually, the cited position of the MPEP does not obviate the requirement that a combination of references can be used to support a rejection of claims as obvious only upon showing a suggestion or motivation to make the specific combination

claimed. In addition, the examiner has failed to identify a explicit suggestion in the prior art to combine the references or to provide the requisite evidence of a scientific rationale for combining the references.

Alas teaches that the C2B8 antibody can be used to sensitize B cell lymphoma cells to cytotoxic agents. Alas observed that cells treated with C2B8 downregulate the expression of IL10. Based thereon, Alas postulated that the C2B8 antibody is effective based on regulation of IL10, which in turn regulates cellular apoptotic proteins.

The examiner states that "because addition of C2B8 resulted in downregulation of IL10 after 72 hours, [sic] it would be obvious to add anti-IL10 antibody to remove IL10 from the cells prior to the 72 hours." Official action, page 4. **Despite the examiner's proposed use of an anti-IL10 antibody, Alas does not describe use of an anti-IL10 antibody in any capacity, including any therapeutic capacity, let alone in combination with a B cell depleting antibody for treatment of B cell lymphoma as now claimed. Thus, a specific suggestion or motivation to perform the claimed invention is absent from Alas.**

The examiner suggests that results as to the mechanism of C2B8 therapy, which include downregulation of IL10, support his argument that a skilled artisan would have been motivated to perform the presently claimed combination therapy. However, no evidentiary support is offered to attest to the scientific reasonableness or desirableness of this suggestion. Rather, the proposed combination is merely that of the examiner. Unpredictability in the art of cancer therapies with respect to the role of cytokines, as described below, supports that the suggestion of the examiner would be considered mere speculation in the absence of evidentiary support in the form of experimental results.

The deficiency of Alas is not cured by the disclosure of Levy. Levy teaches that IL10 enhances cell viability by inducing bcl-2 expression. This protective effect is abolished on addition of an anti-IL10 antibody. Levy uses an anti-IL10 antibody to demonstrate the specificity of IL10-induced cell protection and to implicate IL10 in human pathology. No data is presented regarding *in vivo* activity of the disclosed anti-IL10 antibody. Further, Levy does not even suggest *in vivo* or therapeutic use of the disclosed anti-IL10 antibody. The mere existence of an IL10 antagonist (*e.g.*, anti-IL10 antibody), as described by Levy, does not suggest or motivate an unobvious therapeutic use of that antibody.

The deficiency of Alas is also not cured by the disclosure of Goldenberg. Goldenberg describes treatment of B cell malignancies using an anti-CD22 antibody in combination with

chemotherapeutics. The examiner relies on Goldenberg as teaching multimodal therapy, including administration of an anti-CD22 antibody in combination with cytokines, such as IL10 (claim 15). In contrast to Goldenberg, the present invention teaches combination therapies that include the use of IL10 antagonists. The examiner dismisses previously submitted arguments as directed only to the position that Goldenberg does not teach the combination of therapies which include an IL10 antagonist. Official action, page 4. While the examiner's use of the reference as illustrative of multimodal therapy is understood, the examiner has improperly ignored the teachings of the multimodal therapy described therein, which in fact *teach away* from the presently claimed invention, as described further below.

II. Knowledge In The Art At The Time Of The Instant Invention Taught Away From The Use of Anti-IL10 Antibodies For Cancer Therapy

Applicant further submits that, at the time of the instant invention, the use of IL10 antagonists in cancer therapy was controversial. The literature contained reports that both supported and discounted a correlation between cytokines and disease progression. For example, Bonnefoix et al. (1997) *Leuk Lymphoma* 25:169-178 (Bonnefoix) found that cytokines (IL2, IL3, IL4, IL6, IL10, IL13, G-CSF, GM-CSF, interferon alpha and interferon gamma) could either inhibit or stimulate proliferation of lymphoma cells of various histological subtypes.

The examiner discounts Bonnefoix as irrelevant as failing to teach any IL10 antagonists. Official action, page 5, lines 3-7. Applicant responds that Bonnefoix teaches the unpredictability of the role of cytokines in cancer.

In further support thereof, Goldenberg, disclosed cancer therapies comprising administration of an anti-CD22 antibody in combination with cytokines, including IL10 (*not* IL10 antagonists as presently claimed). Similarly, U.S. Patent No. 5,770,190 to Bruserud et al. (Bruserud) suggests administration of IL10 (*not* IL10 antagonists as presently claimed) in conjunction with chemotherapeutic agents for treatment of acute leukemia.

Thus, knowledge in the art at the time of the instant invention did not clearly identify anti-IL10 as a possible treatment for lymphoma. By contrast, the teachings of Bonnefoix, Goldenberg, and Bruserud *teach away* from antagonism of IL10 as a useful therapeutic approach.

The examiner states that "it is clear from the prior art in the rejection cited that IL10 is important for cancer therapy and regulates bcl-2." Official action, page 5, lines 5-7. **While**

suggestive of a mechanism by which existing cancer therapies may be effective, the cited art, does not elucidate the use of an anti-IL10 antibody for the treatment of B cell lymphoma.

III. The Examiner Has Improperly Used An Obvious-To-Try Standard

The examiner's suggestion that anti-IL10 therapy be combined with administration of a C2B8 antibody is at best a proposal to try the combination, which is an improper standard for determining obviousness. The Federal Circuit has consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C. § 103. *See e.g., In re O'Farrell*, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680 (Fed. Cir. 1988). The end result of a pursuit is not obvious simply because it may be obvious to try to achieve such a result.

In the instant case, the examiner's conclusion that the instant methods are obvious "because combination therapy has been shown to treat cancers effectively" is a mere invitation to try any combination of existing combination therapies to thereby arrive at an effective treatment regimen. Any perceived ease or ensured success in such combination is flawed, given potential adverse interactions among drugs and the persistent difficulty in treating cancer. The resulting improved therapeutic method, which is a combination of existing methods, and which combination yields unexpected efficacy for treating B cell lymphoma, is not obvious simply because it may have been obvious to try *any* combination of existing methods.

IV. The Claimed Methods Produce Unexpected Results

Applicant further responds that the present invention produces synergistic effects not predicted by the sum of the individual therapies. The Court of Appeals for the Federal Circuit has repeatedly held that secondary considerations such as unexpected results can effectively rebut a finding of *prima facie* obviousness. *See e.g., In re Geisler*, 116 F.3d 1465, 1469, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1997) (quoting *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). Thus, even assuming *arguendo* that a *prima facie* case of obviousness has been established, the unexpected and synergistic qualities of the presently claimed combination are sufficient to overcome the examiner's finding.

The studies by Alas suggest that the effects of C2B8 are mediated by resultant changes in 1L10. Based on these results, treatment with an IL10 antagonist would be expected to be redundant to treatment with C2B8. Specifically, the use of C2B8 in conjunction with an IL10

antagonist would be expected to have no greater therapeutic benefit than the use of C2B8 alone. As disclosed in the instant application, the proposed combination yielded unexpected synergistic results (see e.g., page 10, lines 5-8, page 13, lines 1-8).

The rejection of claims based on obviousness is effectively overcome by unexpected superior efficacy of the invention. A greater-than-additive clinical response, as now observed when a B cell depleting antibody is combined with an anti-IL10 antibody, was unpredicted prior to disclosure of the instant application. The unexpected results achieved using the presently claimed inventive methods is sufficient to rebut a rejection of claims based on a prior suggestion or motivation to perform the methods, notwithstanding applicant's arguments that such combination is not suggested or motivated by the prior art, herein above.

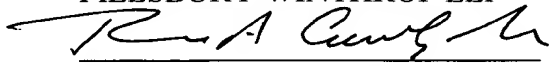
Based on the foregoing arguments, the teachings of Alas, Levy, and Goldenberg, when considered alone or in combination, fail to motivate the use of an anti-CD20 antibody in combination with IL10 antagonists as recited in the instant claims. Claims 74, 76-79, and 83 are believed to be unobvious over the cited references in accordance with 35 U.S.C. § 103(a). Claims 75, 81-82, 84-87, and 89-96 ultimately depend from claims 74, 76-79, and 83 and are therefore also believed to be patentably over the cited references. Thus, applicant respectfully requests that the rejection of claims 74-79, 81-87, and 89-96 under § 103(a) be withdrawn.

Conclusion

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP



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